Dapsone-induced agranulocytosis in a patient of leprosy

Sir,

Agranulocytosis is a rare but fatal complication of dapsone and should be diagnosed early and treated accordingly as early measures can be life-saving for the patient. Dapsone is the prototype of sulfones. It is used as a primary drug for leprosy[1] and is also used in several inflammatory dermatoses like dermatitis herpetiformis, erythema elevatum diutinum, acne conglobata, bullous lesions in lupus erythematosus and infections like actinomycetoma, *P. carinii* pneumonia and falciparum malaria.[2,3]

The adverse profile of dapsone includes hemolysis and methemoglobinemia which are usually pharmacologic at doses of >50 mg/day. Other side-effects are peripheral neuropathy, hepatitis, sulfone syndrome and rarely, hypoalbuminemia and psychosis.

Agranulocytosis is a rare complication but very serious toxic effect of the sulfones.[1] It has been reported to occur in 0.2-0.4% of patients treated with dapsone.[4] It is reported rarely with dapsone when used alone and is more common when dapsone is used with other agents in the prophylaxis of malaria.

A 25-year-old man presented to us with an erythematous plaque over the left eye since four months. Routine blood investigations were normal. Skin biopsy showed features of borderline tuberculoid leprosy. Skin smear revealed bacteriological index of 1+. Based on the above findings, the patient was categorized as borderline tuberculoid leprosy with Type I reaction with facial nerve involvement and was started on multidrug therapy and daily 60 mg of prednisolone. The patient presented again with high fever, tachypnea, hypotension, pharyngeal congestion, dyspnea, cough, and lymphadenopathy (cervical, inguinal, axillary). Chest examination revealed bilateral coarse crepitations over both lower lungs. There were a few purpuric cutaneous lesions over the right upper limb. Blood culture showed *Staphylococcus aureus*.

Chest X-ray revealed bilateral lower lobe consolidation. Total count was 700/cmm with peripheral smear showing agranulocytosis. Patient was diagnosed as a case of pneumonia superimposed over agranulocytosis and was transferred to medicine ICU. He was treated with vasopressors, Linezolid (600 mg IV 12 hourly) and amikacin (15 mg/kg) and was given granulocyte colony stimulating factor (G-CSF) in a dose of 5 μg/kg. Granulocyte count became

normal after seven days of treatment. Treatment with G-CSF was continued for a total of nine days. Patient's condition improved rapidly after starting G-CSF and he was discharged later.

Agranulocytosis is an acute condition where there is a sudden drop in white cell production leaving the body susceptible to bacterial invasion and septicemia.[6] It is reported to occur in 0.2-0.4% of patients treated with dapsone. Though reversible, the condition can be fatal due to the occurrence of septicemia or infections.

In the majority of cases, its occurrence is due to sensitization to the drug which depresses the formation of granulocytes in the bone marrow.[5] The mechanism postulated for the sensitization is the formation of hydroxylamine, the toxic metabolite of dapsone which is also responsible for methemoglobinemia and hemolysis.[6] Another possible mechanism being the formation of antibodies for neutrophil progenitors in the bone marrow and the resultant destruction producing agranulocytosis.[6] Agranulocytosis due to dapsone is not dose-related and when severe, can also involve platelets.[3]

Neutropenia is noticed earliest at three weeks and the onset almost always occurs within three months.[3] Fever and ulcerating pharyngitis, pallor, in a patient on the first few months of dapsone should be taken as warning symptoms and agranulocytosis should be excluded in such cases.[7]

Dapsone can produce agranulocytosis in other conditions besides dermatitis herpetiformis like leprosy, linear IgA dermatosis, cicatricial pemphigoid, rheumatoid arthritis, leukocytoclastic vasculitis, and even when given for malaria prophylaxis,[3,6,8] The rare nature of this side-effect and associated drugs like prednisolone account for the late detection of this complication and the resulting fatality.

In our patient, early treatment with antibiotics and G-CSF accounted for the survival of the patient. It is recommended that a patient should be cautioned about the development of infection and fever during the initial part of dapsone treatment.[2] A review shows this side-effect to be population-sensitive.[5] To detect the complication early, a leukocyte count with a differential and hemoglobin levels should be done weekly for the first month of therapy, twice monthly for the next two months, and periodically thereafter.[2] Liver and renal function tests are also conducted, before therapy and periodically later. However, the rarity of this complication makes such testing difficult to follow as a routine.

Fatality in different case reports has been 20%.[5] This fatal condition should be diagnosed early and treated accordingly as early measures can be life-saving for the patient.

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